Approval Package for:

Application Number: 040110

Trade Name: MEPERIDINE HCL TABLETS USP

Generic Name: Meperidine Hcl Tablets USP

Sponsor: Roxane Laboratories, Inc.

Approval Date: March 12, 1997

APPLICATION 040110

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	Included	Pending	Not	Not
		Completion	Prepared	Required
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Application Number 040110

APPROVAL LETTER

MAR 1 2 1997

Roxane Laboratories, Inc.
Attention: Sue T. Bastaja, R.Ph., J.D.
P.O. Box 16532
Columbus, OH 43216-6532

Dear Madam:

This is in reference to your abbreviated new drug application dated July 25, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Meperidine Hydrochloride Tablets USP, 50 mg and 100 mg.

Reference is also made to your amendments dated May 16, 1996, and January 15, and March 10, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Meperidine Hydrochloride Tablets USP, 50 mg and 100 mg, to be bioequivalent and, therefore, therapeutically equivalent to those of the listed drug (Demerol® Tablets, 50 mg and 100 mg, respectively, of Sterling Winthrop Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

3/12/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPLICATION NUMBER 040110

FINAL PRINTED LABELING

Usual Dosage: See Package Insert for Complete Prescribing Information.

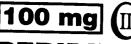
> Store at Controlled Room Temperature 15°-30°C (59°-86°F)

Dispense in a well-closed light-resistant container as defined in the USP.





NDC 0054-4587-29 500 Tablets



MEPERIDINE

Hydrochloride Tablets USP

Each tablet contains
Meperidine Hydrochloride 100 mg
(Warning: May be habit forming)

Caution: Federal law prohibits dispensing without prescription.

Usual Dosage: See Package Insert For Complete Prescribing Information.



Store at Controlled Room Temperature
15, 70°F (59°-96°F)
Dispense in a well-closed, light-resistant container as defined in the USP.



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゚ヮヹ

NDC 0054-8584-11

25 Tablets (Reverse-Numbered)

Tablets USP

Each tablet contains: Meperidine Hydrochloride 50 mg (WARNING: May be habit forming)

Caution: Federal lew prohibits dispensing without prescription.

Store at Controlled Room Temperature 15°-30° C (59°-86°F). Protect From Light.

Usual Dosage: See Package Insert For Complete Prescribing Information.

Blisters are not child-resistant. Use child-resistant closure if dispensing to outpetient.

2 1997

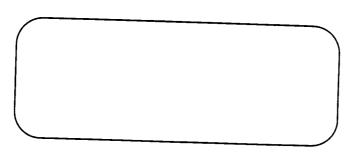
TABLETS IDENTIFIED

54 879

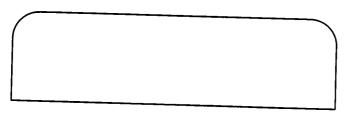


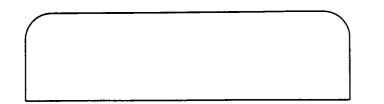
4023920

056 © RLI, 1996



RETURNED DOSE POCKET





1 2 1997

NDC 0054-8587-11

25 Tablets (Reverse Numbered)



Each tablet contains: Meperidine Hydrochloride 100 mg
(WARNING: May be habit forming)

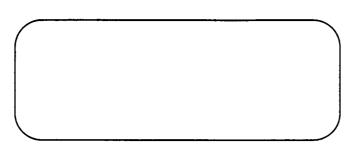
Caution: Federal lew prohibits dispensing without prescription.
Store at Controlled Room Temperature 15*-30* C (58*-86*F). Protect From Light.
Usual Disage: Se Package insert For Complete Prescribing Information.
Blisters are not child-resistant. Use child-resistant closure if dispensing to outpatient.

TABLETS IDENTIFIED

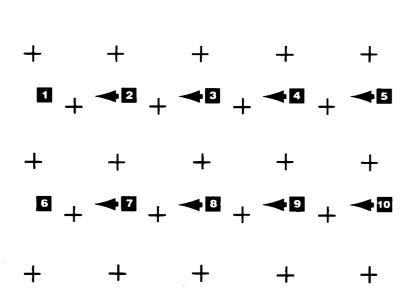
54 163



4023930 056 © RLI. 1996



RETURNED DOSE POCKET





MEPERIDINE HYDROCHLORIDE TABLETS USP



017

4056205

44

ROXANE LABORATORIES, INC.

MEPERIDINE HYDROCHLORIDE (II) TABLETS USP

DESCRIPTION

Each tablet contains:

Meperidine Hydrochloride....... 50 mg, 100 mg (WARNING: May be habit forming)

Meperidine hydrochloride is ethyl 1-methy-4phenylisonipecotate hydrochloride, a white crystalline substance with a melting point of 186°C to 189°C. It is readily soluble in water and has a neutral reaction and a slightly bitter taste. The solution is not decomposed by a short period of boiling. Meperidine hydrochloride may be represented by the following structural formula:

C,5H2,NO2 • HCI

M.W. 283.80

Meperidine hydrochloride tablets are supplied for oral administration containing 50 mg or 100 mg meperidine hydrochloride and the following inactive ingredients: starch (corn), lactose monohydrate, povidone, microcrystalline cellulose, pregelatinized starch, croecarmellose sodium, and magnesium steerate

CLINICAL PHARMACOLOGY

Meperidine hydrochloride is a narcotic analgesic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation.

of therapeutic value are analgesia and sedation. There is some evidence which suggests that meperioline may produce less amooth muscle spasm, constipation, and depression of the cough reflex than equianalgesic doses of morphine. Mepridine, in 60 to 80 mg parenteral doses, is approximately equivalent in analgesic effect to 10 mg of morphine. The onset of action is slightly more rapid than with morphine, and the duration of action is slightly shorter. Meperidine is significantly less effective by the oral than by the parenteral route, but the exact ratio of oral to parenteral effectiveness is unknown.

INDICATIONS AND USAGE

Meperidine hydrochloride tablets USP are indicated for the relief of moderate to severe pain.

CONTRAINDICATIONS

Hypersensitivity to meperidine.

Meperidine is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or those who have recently received such agents. Therapeutic doses of meperidine have occasionally precipitated unpredictable, severe, and occasionally fatal reactions in patients who

CONTRAINDICATIONS

Hypersensitivity to meperidine

Meperidine is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or those who have recently received such agents. Therapeutic doses of mependine have occasionally precipitated unpredictable, severe, and occasionally fatal reactions in patients who have received such agents within 14 days. The mechanism of these reactions is unclear, but may be related to a preexisting hyperphenylalaninemia. Some have been characterized by coma, severe respiratory depression, cyanosis, and hypotension, and have resembled the syndrome of acute narcotic overdose. In other reactions the predominant manifestations have been hyperexcitability, convulsions, tachycardia, hyperpyrexia, and hypertension. Although it is not known that other narcotics are free of the risk of such reactions, virtually all of the reported reactions have occurred with meperidine. If a narcotic is needed in such patients, a sensitivity test should be performed in which repeated, small, incremental doses of mor-Phine are administered over the course of several hours while the patient's condition and vital signs are under careful observation. (Intravenous hydrocortisone or prednisolone have been used to treat severe reactions, with the addition of intravenous chlorpromazine in those cases exhibiting hypertension and hyperpyrexia. The usefulness and safety of narcotic antagonists in the treatment of these reactions is unknown.)

WARNINGS

Drug Dependence: Meperidine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of meperidine, and it should be prescribed and administered with the same degree of caution appropriate to the use of morphine. Like other narcotics, meperidine is subject to the provisions of the Federal narcotic laws.

INTERACTION WITH OTHER CENTRAL MERVOUS SYSTEM DEPRESSANTS: MEPERIONE SHOULD BE USED WITH GREAT CAUTION AND IN REDUCED DOSAGE IN PATIENTS WHO ARE CONCURRENTLY RECEIVING OTHER NARCOTIC ANALGESICS, GENERAL ANESTHETICS, PHENOTHIAZINES, OTHER TRANQUILIZERS (see Dosage and Administration), SEDATIVE-HYPNOTICS (INCLUDING BARBITURATES), TRICYCLIC ANTIDEPRESSANTS, AND OTHER CNS DEPRESSANTS (INCLUDING ALCOHOL), RESPIRATORY DEPRESSION, HYPOTENSION, AND PROFOUND SEDATION OR COMA MAY RESULT.

Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of meperidine and its capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial resions, or a preexisting increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries. In such patients, meperidine must be used with extreme caution and only if its use is deemed essential.

Asthma and Other Respiratory Conditions: Mependine should be used with extreme caution in patients having an acute asthmatic attack, patients with chronic obstructive pulmonary disease or cor pulmonale, patients having a substantially decreased respiratory reserve, and patients with preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive white simultaneously increasing airway resistance to the point of apnea.

Hypotensive Effect: The administration of mependine may result in severe hypotension in the postoperative patient or any individual whose ability to maintain blood pressure has been compromised by a depleted blood volume or the administration of drugs such as the phenothiazines or certain anesthetics.

Usage in Ambulatory Patients: Meperidine may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient should be cautioned accordingly.

Meperidine, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

Usage in Pregnancy and Lactation: Meperidine should not be used in pregnant women prior to the labor period, unless in the judgment of the physician the potential benefits outweigh the possible hazards, because safe use in pregnancy prior to labor has not been established relative to possible adverse effects on fetal development.

Meperidine appears in the milk of nursing mothers receiving the drug.

PRECAUTIONS

Supraventncular Tachycardias: Meperidine should be used with caution in patients with atrial flutter and other supraventricular tachycardias because of a possible vagolytic action which may produce a significant increase in the ventricular response rate.

Convulsions: Meperidine may aggravate preexisting convulsions in patients with convulsive disorders. If dosage is escalated substantially above recommended levels because of tolerance development, convulsions may occur in individuals without a history of convulsive disorders.

Acute Abdominal Conditions: The administration of meperidine or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special Risk Patients: Mependine should be given with caution and the initial dose should be reduced in certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism. Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS

The major hazards of meperidine, as with other narcotic analgesics, are respiratory depression and, to a lesser degree, circulatory depression; respiratory arrest, shock, and cardiac arrest have occurred.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not experiencing severe pain. In such individuals, lower doses are advisable. Some adverse reactions in ambulatory patients may be allevialed if the patient lies down.

Other adverse reactions include:

Nervous System: Euphoria, dysphona, weakness, headache, agitation, tremor, uncoordinated muscle movements, transient halucinations and disorientation, visual disturbances.

Gastrointestinal: Dry mouth, constipation, biliary tract spasm.

Cardiovascular: Flushing of the face, tachycardia, bradycardia, palpitation, hypotension (see WARNINGS), syncope.

Genitourinary: Urinary retention.

Allergic: Pruritus, urticaria, other skin rashes.

Other: Antidiuretic effect.

OVERDOSAGE

Symptoms: Serious overdosage with meperidines is characterized by respiratory depression (a decrease in respiratory rate and/or total volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeleral muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment: Primary attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. The narcotic antagonist, naloxone hydrochloride, is a specific anticote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including meperidine. Therefore, an appropriate dose of this antagonist should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

In case of overdosage with meperidine tablets, the stomach should be evacuated by emesis or gastric lavage.

NOTE: In an individual physically dependent on narcotics, the administration of the usual dose of a narcotic antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonists administered. The use of narcotic antagonists in such individuals should be avoided if possible. If a narcotic antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and only one-fifth to one-tenth the usual initial dose administered.

pendence and the cose of antagonist administered. The use of narrotic antagonists in such individuals should be avoided if possible. If a narrotic antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be administered with extreme care and only one-fifth to one-tenth the usual initial dose administered.

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to the severity of the pain and the response of the patient. Mependine is less effective orally than with parenteral administration. The dose of meperidine hydrochloridg should be proportionately reduced (usually by 25 to 50 percent) when administered concomitantly with phenothiazines and many other tranquitizers since they potentiate the action of meperidine.

Adults: The usual dosage is 50 to 150 mg orally every 3 or 4 hours as necessary.

Children: The usual dosage is 0.5 to 0.8 mg/lb orally up to the adult dose, every 3 or 4 hours as necessary.

HOW SUPPLIED

Meperidine Hydrochloride Tablets USP are available for oral administration as:

50 mg white, scored tablets
(Tablets Identified 54 879)
NDC 0054-8584-11: Unit dose, 25 tablets per card
(reverse numbered).
NDC 0054-4584-25: Bottles of 100 tablets.
NDC 0054-4584-29: Bottles of 500 tablets.
100 mg white, scored tablets
(Tablets Identified 54 183)
NDC 0054-8587-11: Unit dose, 25 tablets per card
(reverse numbered).
NDC 0054-4587-25: Bottles of 100 tablets.
NDC 0054-4587-29: Bottles of 500 tablets.

Store at Controlled Room Temperature 15°-30°C (59°-86°F) Dispense in a well-closed, light-resistant container as defined in the USP/NF.

DEA Order Form Required.

Caution: Federal law prohibits dispensing without prescription.

4056205 017 © RLI, 1997 Revised January 1997

Roxan

RN 25 BLISTER LABEL:

MEPERIDINE (II)
Hydrochloride
Tablet USP, 100 mg
LOT 940000 EXP. JAN. 1, 96
Roxane Columbus, OH 43216

APPLICATION NUMBER 040110

CHEMISTRY REVIEW(S)



Food and Drug Administration Center for Drug Evaluation and Research Office of Generic Drugs

Chemistry Division II - Branch VII Abbreviated New Drug Application Review

- 1. CHEMISTRY REVIEW NO. 3
- 2. ANDA # 40-110
- NAME AND ADDRESS OF APPLICANT
 Roxane Laboratories, Inc.
 P.O. Box 16532
 Columbus, OH 43216-6532



4. LEGAL BASIS FOR SUBMISSION
Demerol® Tablets - 50 mg/tablet
Demerol® Tablets - 100 mg/tablet
Sanofi Winthrop Pharmaceuticals
90 Park Avenue
New York, NY 10016

Drug product is Pre-1962 product.

5. <u>SUPPLEMENT(s)</u> N/A

- 6. PROPRIETARY NAME N/A
- 7. NONPROPRIETARY NAME
 Meperidine
 Hydrochloride USP
- 8. <u>SUPPLEMENT(s) PROVIDE(s) FOR:</u> N/A
- 9. AMENDMENTS AND OTHER DATES:

Firm:

7/25/94 Original submission

8/17/94 Amendment - Response to Agency's letter of

8/12/94, submission of certification

for third copy.

5/31/96 Amendment - Response to Agency's letter of 2/14/95.

1/15/97 Amendment - Response to Agency's letter of 12/11/96.

FDA:

8/12/94 Refusal to File letter issued.

9/2/94 Receipt acknowledged, acceptance for filing,

8/18/94.

2/14/95 Issuance of Not Approvable letter.

9/30/96 Issuance of No Further Questions, Division of

Bioequivalence.

12/11/96 Issuance of Not Approvable letter.

10. PHARMACOLOGICAL CATEGORY Narcotic Analgesic 11. Rx or OTC Rx

12. RELATED IND/NDA/DMF(s)

13. <u>DOSAGE FORM</u>
Tablet for oral administration

14. <u>POTENCIES</u> 50 mg and 100 mg

15. CHEMICAL NAME AND STRUCTURE

Meperidine Hydrochloride USP C₁₅H₂₁NO₂.HCl; M.W. = 283.80

Ethyl 1-methyl-4-phenylisonipecotate hydrochloride.

CAS [50-13-5]

A white crystalline substance, mp 186 - 189°C, slightly bitter taste. Stable to air. Just acid to litmus (1:10 soln). Soluble in water, acetone, ethyl acetate; slightly soluble in alcohol, isopropanol. Insoluble in benzene, ether. Aqueous solutions may be sterilized by boiling for shore periods without decomposition. LD₅₀ orally in rats: 170 mg/kg.

16. RECORDS AND REPORTS

11/23/94 - Review of Dissolution Data and Waiver Request, Division of Bioequivalence, J. Lee.

1/3/95 - Labeling review, C. Zimmerman.

1/5/95 - Chemistry Review #1, G.J. Smith.

8/16/96 - Labeling review, C. Hoppes.

9/26/96 - Review of Dissolution Data and Waiver Request for new drug substance manufacturer, Division of Bioequivalence, J. Lee.

11/1/96 - Chemistry Review #2, G.J. Smith.

2/20/97 - Labeling review, J. White.

17. <u>COMMENTS</u>

The firm has resolved all major questions concerning the chemistry, manufacturing, and controls section of the application.

Labeling was found to be satisfactory.

Waiver granted by the Division of Bioequivalence.

Acceptable EIR issued by the Office of Compliance.

Methods validation not required since drug substance and product are compendial.

DMF for the drug substance satisfactory.

- 18. <u>CONCLUSIONS AND RECOMMENDATIONS</u>
 The application may be Approved.
- 19. REVIEWER: DATE COMPLETED: February 26, 1997

ANDA APPROVAL SUMMARY

ANDA: 40-110 DRUG PRODUCT: Meperidine Hydrochloride USP

FIRM: Roxane DOSAGE FORM: Tablet STRENGTHS: 50 mg

P.O. Box 16532 100 mg

Columbus, OH 43216-6532

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP statement (p. 126) and Section 306(k) certification (p. 128) in original submission.

EIR acceptable for drug product manufacturer and drug substance manufacturer, 1/17/97.

Facilities included:

Manufacturing, testing, packaging, labeling, and stability testing:

Roxane Laboratories, Inc. 1809 Wilson Road Columbus OH 43228.

Drug Substance Manufacturer:

BIO STUDY:

A waiver of *in vivo* bioequivalence study was granted by the Division of Bioequivalence, J. Lee, 11/23/94, for drug product using Nycomed as the drug substance source.

Dissolution testing results were found to be acceptable and the firm's product was deemed bioequivalent to the reference product, Demerol® Tablets 50 mg and 100 mg manufactured by Sterling Winthrop, by the Division of Bioequivalence, J. Lee, 11/23/94.

The firm submitted dissolution data for exhibit lots of drug product manufactured using drug substance from their new supplier, Mallinckrodt.

Dissolution testing results were found to be acceptable for Lots #959034, batch size tablets, and #959019, batch size tablets, and the firm's product was deemed equivalent by the Division of Bioequivalence, J. Lee, 9/26/96.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Drug substance and drug product are compendial.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability for the following included:

<u>Dosage</u> 50 mg	<u>Lot </u> 959034	100's 40°C/75%		Test Conditions 40°C/75% RH/3 months 25° - 30°C/6 months
100 mg	959019		100's 500's	40°C/75% RH/3 months 25° - 30°C/12 months

Container/Closure system:

Expiration date: 24 months based on accelerated data.

LABELING:

Description in package insert satisfactory for molecular structure, molecular formula, formula weight, inactive ingredients, product description and package size.

Professional labeling - satisfactory, J. White, 2/20/97.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Bio waiver batch: 100 mg product, Lot #959019, batch size tablets, stability data included.

Bio waiver batch: 50 mg product, Lot #959034, batch size tablets, stability data included.

DMF Malinckrodt, satisfactory, D. Shostak, 7/3/96, no amendments since then.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

See above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?:

Executed batch records for the 50 mg (bio waiver/stability batch), and the 100 mg (bio waiver/stability batch) included. Four blank batch records were submitted in the application:

x 100 mg policy.

tablets. All scale-ups consistent with current Office policy. Proposed manufacturing processes are the same as the bio/stability batches.

CHEMIST:

DATE: 4-23-97

SUPERVISOR:

DATE: 2/25/67

APPLICATION NUMBER 040110

BIOEQUIVALENCE REVIEW(S)

ANDA 40-110

Roxane Laboratories, Inc. Attention: Donald H. Chmielewski P.O. BOX 16532 Columbus OH 43216

SEP 3.0 (838)

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Meperidine Hydrochloride Tables USP, 50 mg and 100 mg.

- 1. The Division of Bioequivalence has completed its review and has no further questions at this time.
- 2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Meperidine HCl 50 and 100 mg Tablet NDA #40-110 Reviewer: J. Lee 40110D.596 Roxane Laboratories, Inc. Columbus, Ohio Submission date: May 31, 1996

Review of Dissolution Data for Change of Supplier of New Drug Substance

The sponsor has previously submitted (7/25/94) dissolution data for their test products vs Demerol[®] and requested waiver of in-vivo requirements. The Division of Bioequivalence granted that waiver based on test results. Subsequently, the ownership of the originally cited DMF for the new drug substance was transferred to another firm thereby invalidating the letter of authorization to reference that DMF.

The sponsor now has a new supplier of the active ingredient and has submitted dissolution data from tablets manufactured with the new supplier's ingredient vs Demerol[®].

This drug product is AA listed in the Orange Book.

Comment:

1. The dissolution profiles show that at the 15 minute sampling interval the test products are completely dissolved, while the Demerol tablets are not dissolved until the 30 minute sampling time. Both products, however, comfortably meet the Q of NLT dissolved in 45 minutes.

Recommendation:

- 1. The dissolution testing conducted on the 50 and 100 mg tablets, batch #939134 and 939135, respectively, is acceptable.
- 2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 ml of water at 37°C using USP XXIII apparatus I (basket) at 100 rpm. The test product should meet the following specification:

Not less than of the labeled amount of the drug in the tablet is dissolved in 45 minutes.

The Division of Bioequivalence deems the test product manufactured using the Mallinkrodt supplied drug substance equivalent to the previous test product manufactured using the Sterling Winthrop supplied drug substance.

9/25/96

J. Lee

Division of Bioequivalence

Review Branch II

RD INITIALED SNERURKAR

FT INITIALED SNERURKAR

9/26/96

Concur:

Keith Chan, Ph.D.

Director, Division of Bioequivalence

JLee/jl/ 09-10-96

cc: NDA #40-110 (original, duplicate), HFD-630, HFD-655 (Lee, Patnaik), Drug File, Division File

Date:

USP XXIII	Apparatus <u>I</u>	_ Basket _	X	Paddle	rpm1	00	
Medium:	water			Vo	olume: <u>50</u>	<u>0</u> ml .	
Number of	Tabs/Caps Teste	ed: <u>12</u>					
Reference l	Drug: <u>Demerol</u> ®	tablet					
Assay Metl	hodology:			·			
Results				50 mg			
Time	Test Produc	t			Reference	Product	
	Lot # <u>95903</u>	4			Lot #_ 6]	6FJ	
	Mean % Dissolved	Range		(CV)	Mean % Dissolved	_	(CV)
15	_ 98			(1.5)	80		(14)
30	99			(1.8)	98		(5.7)
45	101			(1.9)	104		(3.4)
				()			()
		<u></u>	-	()		-	('
				()			()
	Lot # <u>9590</u>	19		<u>100 mg</u>	Lot # <u>K</u>	P378	
15	92	· —		(2.3)	82		(8.1)
30	93	_		(2.3)	97	- <u>-</u> ,	(1.9)
<u>45</u>	95	_		(2.0)	99		(2.1)
				()	·		()
				()			()
				()			()

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OFFICE OF GENERIC DRUGS DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 40-110 SPONSOR: ROXARE Labore toris
DRUG: meperidine HC/
DOSAGE FORM: tablet
STRENGTHS/(s): 50 mg + 100 mg
TYPE OF STUDY: Single Multiple Fasting _ Fed // A
STUDY SITE:
NOT 15t Generie
STUDY SUMMARY.
Waiver premainly granted on NOJ 23, '9x by DBE.
Present submission (may 31, 96) is acceptable to for
supplier of new drug suletonce. Drug product is AA.
DISSOLUTION: N/A
PRIMARY REVIEWER: Jenny Lee BRANCH: II
INITIAL:DATE 9/25/96
TEAM LEADER: s. Nerurkar, Ph.D BRANCH: II
INITIAL: JATE 9/25/76
DIRECTOR, DIVISION OF BIOEQUIVALENCE: Keith Chan, Ph.D
INITIAL: DATE PAST92
DIRECTOR, OFFICE OF GENERIC DRUGS:
INITIAL: DATE